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PATENT

#30/REPLY BRIEF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of)
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ECKSTEIN *et al.*)
)
Serial No. 08/936,657)
)
Filed: August 16, 1995)

Group Art Unit: 1635

Examiner: LeGuyader, J.

Atty. Docket No.: 00-838A (228/231)

For: **MODIFIED RIBOZYMES**

REPLY TO EXAMINER'S ANSWER

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This Reply is in response to the Examiner's Answer mailed on December 18, 2000. In view of the Federal Holiday on Monday, February 19, Applicant's Reply is due on February 20, 2001.

Claims 44-57 stand rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Applicant maintains its prior arguments set forth in the Appeal Brief dated November 15, 2000.

Under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, the specification must teach one skilled in the art how to cleave a target RNA molecule with a catalytic RNA molecule under conditions suitable for the catalytic RNA molecule to cleave the target RNA molecule, wherein the catalytic RNA molecule comprises at least one modified nucleoside selected from the group consisting of halo, sulfhydryl, azido, amino, monosubstituted amino and disubstituted amino group at the 2' hydroxy position on the ribose sugar. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01.

The specification teaches how to make and use an active catalytic RNA molecule

To satisfy the enablement requirement, the specification must teach one skilled in the art how to make a catalytic RNA molecule comprising at least one modified nucleoside selected from the group consisting of halo, sulfhydryl, azido, amino, monosubstituted amino and disubstituted amino group at the 2' hydroxy position on the ribose sugar and how to cleave a target RNA with said catalytic RNA molecule. The Office admits that Appellant teaches the synthesis of modified ribozymes comprising halo, sulfhydryl, azido, amino, monosubstituted amino, and disubstiututed amino modifications (page 5, Examiner's Answer). However, it alleges that the teaching does not enable the synthesis of an "active" ribozyme having catalytic activity. In contrast to the Office's allegation, the specification teaches the synthesis of several modified catalytic RNA molecules having catalytic activity. Specifically, Example 3 teaches that a modified catalytic RNA molecule, i.e., 2'-fluorouridine-containing ribozyme and 2'-aminouridine-containing ribozyme, cleaves the substrate oligonucleotide with similar efficiency as an unmodified catalytic RNA molecule (specification at pages 20-21). In addition, Example 4 teaches that 2'-fluorouridine-, 2'-fluorocytidine-, and 2'deoxy-substituted ribozymes cleave HIV-1 LTR RNA (specification at pages 24-26). Further, other studies have shown that modified catalytic RNA molecules made using the methods set forth in the instant specification have catalytic activity (see, for example, Stinchcomb Declaration, paragraphs 9-14). Thus, the specification clearly teaches representative examples of modified catalytic RNA molecules having activity. Under Federal Circuit law, "[i]t is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art." *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991)(citing In re Angstadt, 190 USPQ2d 214 (CCPA)).

In addition to providing specific examples of modified catalytic RNA molecules with catalytic activity, the instant application provides considerable guidance to enable a skilled artisan to make and use additional modified catalytic RNA molecules with catalytic activity. For example, the specification describes in detail how to synthesize the modified catalytic RNA molecule of the claimed method. The specification teaches the various types of modifier groups used to make the modified catalytic RNA molecules throughout the specification and particularly at page 4, lines 17-26 and pages 5-10. For example, the specification teaches that the modifier group is a halo, sulfhydryl, azido, amino, monosubstituted amino or disubstituted amino group (specification at page 4, lines 23-24; page 5, lines 24-27). The specification further teaches preferred halo and substituted amino groups at page 5, lines 27-31. In addition, the specification teaches various locations at which these modified groups can be positioned within the catalytic RNA molecules and provides preferred embodiments of modified catalytic RNA molecules (specification at pages 8-9, and Examples 1-5). The specification also teaches the synthesis of modified catalytic RNA molecules at, for example, page 7, line 25 to page 8, line 5 and at page10, line 19 through page 13, line 26, wherein several detailed methods are described. Example 1 provides an additional specific example of synthesis of a modified catalytic RNA molecule.

Still further, the specification teaches one skilled in the art how to determine whether a particular modification affects the activity of a catalytic RNA molecule. For example, at pages 24-26 (Example 4) Appellant provides assays for determining the activity of a modified catalytic RNA molecule. In addition, other assays for determining catalytic activity were known in the art at the time of filing (see, e.g., Fedor et al., PNAS, 87:1668-1672 (1990); Haseloff et al., Nature,

334: 585-591 (1988)). Based on these teachings, one skilled in the art would have been able to screen modified RNA molecules for catalytic activity as a matter of routine experimentation.

Despite these teachings, the Examiner argues that the skilled artisan would have to engage in undue trial and error experimentation to determine which positions can be modified with a particular modifying moiety so that an active ribozyme can be synthesized. However, as discussed above, the specification teaches assays for determining the activity of a modified catalytic RNA molecule. Furthermore, the preferred catalytic RNA molecules are less than 100 nucleotides in length. It would have been a matter of routine experimentation for one skilled in the art to modify various nucleotides and then test the catalytic activity of the modified RNA using the disclosed methods. The law clearly states that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Moreover, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104 (Fed. Cir. 1985); *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

The specification teaches in vitro and in vivo delivery of active catalytic RNA molecules

The Examiner additionally alleges that in vitro and in vivo delivery methods are not supported by the instantly filed application. However, the Appellant describes suitable

techniques for delivering the catalytic RNA into cells, including, for example, exogenous delivery of a pre-formed synthetic RNA and endogenous delivery of a ribozyme coding gene located on a plasmid (specification at page 3). These and other techniques for delivering nucleic acid molecules into cells were well known in the art at the time of filing the present application, as evidenced by the teachings of Ulmann et al. who describes various in vitro and in vivo methods of oligonucleotide delivery (Ulmann et al., Chemical Reviews, 90:544-579 (June 1990)). Other delivery methods, such as transfection of nucleic acid using calcium phosphate, was well known in the art before the filing of the present application (see, e.g., Sambrook et al., Molecular Cloning, A Laboratory Manual, 2nd Ed., 1989, section 16.32). In addition, the exogenous delivery of nucleic acid into eukaryotic cells using cationic lipids was well known at the time of filing (see, e.g., Malone et al., PNAS, 86:6077-6081 (1989)). Such references are representative of the teachings that were available at the time of filing the instant application and provide sufficient guidance to one of ordinary skill in the art to make and use the present invention. The Federal Circuit clearly states that a patent need not teach, and preferably omits, that which is well known in the art. *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986); MPEP 2164.01.

In addition, the Examiner alleges that Appellant has not provided "any evidence pertaining to efficacy of the ribozyme in any treatment methodology" (page 7, Examiner's Answer). However, the subject matter of the pending claims requires the catalytic RNA molecule to cleave the target RNA (i.e., be active), but does not require a specified level of activity. In this regard, Appellant clearly demonstrates that the modified catalytic RNA molecules of the present invention can cleave target RNA in vitro (see Example 4). Furthermore,

at the time of filing, other in vitro studies such as those described in Cameron et al., demonstrated the activity of catalytic RNA molecules in cell culture (Cameron et al., PNAS, 86:9139-9143 (1989)). One of ordinary skill in the art would recognize that appropriate cell cultures, such as the monkey COS1 cells used by Cameron et al., could be used as a predictive model for in vivo activity. As established by the Federal Circuit, "if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating *unless the Examiner has evidence that the model does not correlate.*" MPEP 2164.02 [emphasis added]; In re Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

More importantly, Appellants have demonstrated that the modified catalytic RNA molecules of the claimed method enhance stability by reducing degradation (see Example 5). Accordingly, there is no reason to believe and the Examiner has not demonstrated that the modified catalytic RNA molecules of the present invention would not have activity in vivo. In fact, given their enhanced stability, one of ordinary skill in the art would expect the catalytic RNA molecules of the present invention to be active in vivo. Such results are, in fact, supported by the studies in the Stinchcomb Declaration, which describes the activity of modified catalytic RNA in various in vitro and in vivo systems. For example, the modified catalytic RNA molecules taught in the instant invention have been shown to cleave MDR-1 RNA in cells, when delivered using cationic lipid delivery methods known at the time of filing (Stinchcomb Declaration at paragraph 9). Also, using known cationic lipid delivery methods, the modified catalytic RNA molecules have been shown to cleave c-myb RNA in cells (Stinchcomb Declaration at paragraph 9). In addition, the modified catalytic RNA molecules have been shown to cleave HIV RNA in CD4+ cells, using calcium phosphate transfection techniques known at

the time of filing (Stinchcomb Declaration at paragraph 11). The Stinchcomb Declaration further demonstrates the activity of the instantly described modified catalytic RNA molecules in several in vivo models as well (Stinchcomb Declaration at paragraphs12-14).

Finally, Appellant points out that the Examiner fails to provide any evidence whatsoever that the instant invention would not work for its intended purpose. In the absence of any technical reasons and/or references to support his reasoning, the Examiner has failed to establish a prima facie case of lack of enablement. MPEP 2164.04

Conclusion

Applicant has provided ample guidance to enable a person skilled to art to synthesize a catalytic RNA with the modifications of the instant invention and to test for its nuclease resistance and catalytic activity under a variety of conditions to systematically determine the nucleotide positions within the ribozyme that tolerate chemical modification because such modified ribozyme would be active to, for example, cleave a target RNA. Using the teachings of the instant invention, therefore, it would have been routine to identify all the positions within the ribozyme that can be modified without significantly altering the catalytic activity of the ribozyme. The specification therefore teaches the synthesis of a chemically modified ribozyme that is not only nuclease resistant but also catalytically active.

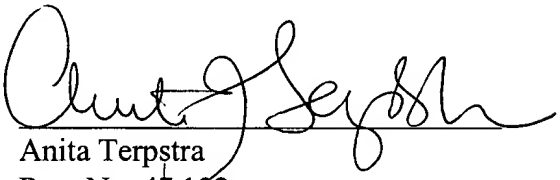
The specification further provides ample guidance to a person skilled in the art to use the chemically modified ribozyme of the invention to cleave a target RNA. Such a ribozyme substituted with the modifications of the instant invention would be catalytically active both *in vitro* and *in vivo*. Although no data is provided in the instant application for the activity of such

chemically modified ribozymes *in vivo*, there is no reason to believe that such ribozymes that are active *in vitro (as shown in the application)*, would not be active *in vivo*. In fact there is ample evidence in the art to show that a chemically modified ribozyme that is catalytically active *in vitro*, is also active *in vivo* (see, for example, the Stinchcomb Declaration and the Appeal Brief filed on November 15, 2000).

On the basis of the foregoing and in view of the arguments presented herein, reversal of the 35 U.S.C. § 112 rejection is appropriate.

Respectfully submitted,

Date: February 20, 2001

By: 

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